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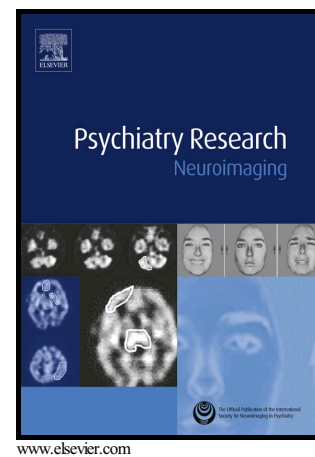
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Age-Related Parieto-occipital and other Gray Matter Changes in Borderline Personality Disorder: A Meta-analysis of Cortical and Subcortical Structures

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Age-Related Parieto-occipital and other Gray Matter Changes in Borderline Personality
Disorder: A Meta-analysis of Cortical and Subcortical Structures

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Abstract

Previous research suggests that core borderline personality disorder (BPD) symptoms increase or decrease in severity with advancing age. While structural neuroimaging studies show smaller limbic and prefrontal gray matter volumes (GMV) in primarily adult and adolescent BPD patients, respectively, findings are inconsistent. Using the effect-size signed differential mapping (ES-SDM) meta-analytic method, we investigated the relationship between advancing age and GMV abnormalities in BPD patients. A total of nine voxel-based morphometry (VBM) studies comparing regional GMV of 256 BPD patients and 272 healthy control subjects were included. Meta-analysis identified lower GMV in the right superior/middle temporal gyri and higher GMV in the right supplementary motor area of BPD patients. Meta-regression showed that increasing

age was significantly associated with increased GMV in the left superior parieto-occipital gyri, with younger-aged patients starting at lower GMV compared to controls. In contrast, increasing age was associated with decreased GMV in the right amygdala. These findings suggest that while GMV deficits in limbic structures may become pronounced with advancing age in the course of BPD, parieto-occipital rather than frontal GMV deficits could be especially prominent in younger-aged BPD patients.

Keywords: voxel-based morphometry, magnetic resonance imaging, neuroimaging, meta-analysis, VBM, MRI, BPD

1. Introduction

Borderline personality disorder (BPD) is defined as a lifelong condition in which environmental factors act upon pre-existing neurobiological substrates to produce a dynamic symptom constellation presenting as significantly impaired affect regulation and psychosocial functioning from early adolescence onward (Chanen and Kaess, 2012; Hughes et al., 2012; Glenn and Klonsky, 2013; Morgan et al., 2013). Crowell's extended biosocial model of BPD (2009) states that biologically-driven temperamental vulnerabilities such as emotional sensitivity and impulsivity interact with an invalidating caregiving environment to produce emotional lability with heightened negative affectivity. In line with Crowell's model, cross-sectional and longitudinal studies of BPD patients suggest that impulsivity/disinhibition tends to peak in adolescence and then sharply decrease in adulthood whereas negative affect either remains stable or steadily increases well into middle adulthood (Stevenson et al., 2003; Paris, 2004; Stepp and Pilkonis, 2008; Arens et al., 2013). This observed age-related symptom presentation is thought to

in part result from specific structural deficits, including decreased gray matter integrity within fronto-limbic structures (Hughes et al., 2012). Specifically, researchers have posited the theory that prefrontal gray matter deficits are present early in the disorder (e.g., adolescence) whereas limbic gray matter deficits develop later in the course of the disorder (e.g., adulthood; Hughes et al., 2012; Goodman et al., 2013).

The theory that gray matter volume (GMV) deficits in BPD are related to age is supported by structural neuroimaging data comparing regional GMV of BPD patients to those of healthy control subjects. When primary structural neuroimaging studies of BPD patients are examined, the majority of the research implicates mainly dorsolateral prefrontal (DLPFC), orbitofrontal (OFC), and anterior cingulate (ACC) damage in adolescents (Chanen et al., 2008; Whittle et al., 2009; Brunner et al., 2010; Goodman et al., 2011) compared to hippocampal and amygdala damage in adults (Soloff et al., 2012; Kuhlmann et al., 2013; Niedtfeld et al., 2013; O'Neill et al., 2013; Rossi et al., 2013; Araujo et al., 2014; Boen et al., 2014). Most published meta-analyses of primary neuroimaging data for BPD patients are restricted to adults; these region-of-interest (ROI) meta-analyses unanimously show hippocampal and amygdala GMV deficits (Nunes et al., 2009; Hall et al., 2010; Rodrigues et al., 2011; de-Almeida et al., 2012; Ruocco et al., 2012). Age-related decreases in GMV in BPD subjects were found in the hippocampus but not the amygdala in a single meta-analysis, supporting the argument that there is age-related neuronal atrophy in the hippocampus (Hall et al., 2010). However, given the lack of neuroimaging meta-analyses focusing on adolescents with BPD pathology, it is difficult to determine whether or not the paucity of primary findings in the hippocampus and amygdala is robust.

The mechanism of the observed fronto-limbic neurodevelopmental pattern in BPD is not yet well understood. Some researchers have hypothesized that initial gray matter deficits in prefrontal regions contribute to the development of limbic system dysfunction over time, as weak prefrontal inhibitory control can lead to hyper-arousal and eventual cellular damage to limbic structures (Chanen et al., 2008). However, since emotional dysregulation is considered the core symptom of BPD (Linehan, 1993), the focus of most neuroimaging meta-analysis has been the amygdala and hippocampus, which precludes the ability to examine the role of prefrontal structures in the etiology of the disorder. Obtaining a comprehensive understanding of GMV as a neurodevelopmental marker in BPD requires meta-analysis of whole-brain voxel-based morphometry (VBM) studies examining adolescent and adult subjects at various developmental stages.

The current whole-brain VBM meta-analysis focuses on age-related cortical and subcortical GMV changes in BPD. Using Effect-Size Signed Differential Mapping (ES-SDM), a coordinate-based meta-analytical method, our study aims were to (1) identify the most consistent areas of lower or higher GMV in BPD patients relative to healthy control subjects and (2) explore whether there are specific regional GMV abnormalities in BPD patients that are age-related.

Drawing from previous research, we hypothesized that lower GMV in limbic regions, particularly the hippocampus and amygdala, would be a robust finding among BPD patients. We additionally hypothesized that a number of cortical regions implicated as central to BPD symptomology would be significantly associated with age. Specifically, we predicted that volumetric deficits in prefrontal regions (i.e., DLPFC, OFC) would be uniquely associated with younger sample mean age, suggesting that these regions are impaired early in the course of BPD

but approach normal volumes as patients age. We further predicted that prominent volumetric deficits in limbic regions (i.e., hippocampus, amygdala) would be associated with older sample mean age, suggesting that these deficits might not be present early in the disorder and develop later on as the disorder progresses.

2. Methods

2.1 Data sources

A systematic and comprehensive literature search was performed to identify whole-brain VBM studies comparing patients with BPD to healthy control subjects. To ensure comprehensiveness, two researchers performed the searches independently using such keywords as “borderline personality,” “neuroimag*,” “mri,” “magnetic resonance,” “brain imaging,” “morphometry,” “voxel,” and “vbm.” One of the researchers performing the searches had received training in database searching at PsycINFO and worked as a database search analyst for six years; this researcher was thus able to use advanced features of databases involved such as Medical Subject Heading terms and controlled vocabulary searching. In addition, reference lists of articles thus obtained were manually checked to identify any additional relevant studies not identified by the computerized search. Potentially included articles were limited to those published online or in print before May 2014.

2.2 Study criteria and data extraction

To be considered for inclusion, studies had to meet the following criteria: (1) published as an original paper in a peer-reviewed journal, (2) reported a GMV (including “gray matter density” or “gray matter concentration”) comparison between patients with BPD and healthy control subjects, (3) used a whole-brain VBM imaging approach, and (4) reported stereotactic coordinates (Talairach or MNI) for whole-brain comparisons of GMV. A study was excluded if

(1) only ROI or small volume correction (SVC) approaches were used, (2) a healthy comparison group was not included, (3) BPD subjects had comorbid neurodegenerative disease, neurodevelopmental disorder, TBI, or psychotic disorder, and (4) the data provided was insufficient even after the author(s) were contacted via email. For each study included in the meta-analysis, peak coordinates of GMV differences found significant at the whole-brain level (no SVCs) were extracted. Coordinate data was independently extracted by two of the article authors to minimize data extraction errors.

Regional gray matter differences between patients with BPD and healthy control subjects were meta-analyzed using the updated anisotropic ES-SDM software, version 4.13 (Radua et al., 2014b). In addition to being statistically validated for use in ES-SDM analysis, anisotropic kernels have been successfully applied in other neuroimaging analyses (Van Hecke et al., 2010; Zhang and Davatzikos, 2013; Radua et al., 2014b). This method has been thoroughly reviewed elsewhere (Radua and Mataix-Cols, 2009; Radua et al., 2012b; Radua et al., 2014b) and is only summarized here.

First, reported peak coordinates and t -values are used to recreate, for each study, a map of the effect size of the comparison between patients and healthy controls. This recreation is based on anisotropic kernels that estimate the effect size of those voxels close to a peak based on the correlation between each of these voxels and the peak, rather than on raw Euclidean distances from the voxels to the peak. Second, a random-effects meta-analysis is separately conducted for each voxel, taking sample size, intra-study variability and between-study heterogeneity into account. Division of meta-analytic effect sizes by their standard errors yields z -values, but these are not normally distributed and thus statistical significance is found using a permutation test.

Previous simulations showed $p \leq 0.005$ (uncorrected) with a cluster-level extent threshold of $k \geq 10$ optimally balance false positives and negatives (Radua et al., 2012b).

A jackknife sensitivity analysis, in which the mean analysis is repeated as many times as the number of tests included while removing one different study each time, was conducted to test the replicability of the results. To examine the effects of age on GMV abnormalities in BPD, a meta-regression was conducted using a more conservative voxel-level threshold of $p \leq 0.0005$ (uncorrected) in accordance with previous meta-analyses (Hart et al., 2012; Radua et al., 2012a; Lim et al., 2014). In line with this conservative approach, we decided to use a cluster-level extent threshold of $k \geq 20$. Supplemental meta-regression and subgroup analyses were conducted to account for potential confounds such as medication effects, MRI processing differences, and comorbid psychiatric conditions. As with our primary age-focused meta-regression analysis, all supplemental analyses were thresholded at $p \leq 0.0005$ (uncorrected) with a cluster-level extent threshold of $k \geq 20$.

3. Results

3.1 Included studies and sample characteristics

After removal of duplicates and obvious irrelevant articles (e.g., animal studies, case reports) the search resulted in a total of 460 abstracts that were examined by two researchers for relevance and inclusion. A total of 51 full-text articles were then retrieved for further review and coding. Of these records, 13 full-text studies met most of the inclusion criteria and were initially considered for meta-analysis. Two articles were later excluded because they were ROI only, and one was excluded because of lack of appropriate control group. Author contact was initiated for one study to obtain necessary coordinate data, but as the author was unable to provide access to the processed data the study was later excluded (Figure 1). The final selection of the nine studies

included in this meta-analysis was achieved by at least the consensus of two of the primary investigators regarding all inclusion and exclusion criteria.

The nine studies included in this meta-analysis comprised 256 BPD patients and 272 healthy comparison subjects (Rusch et al., 2003; Soloff et al., 2008; Brunner et al., 2010; Bertsch et al., 2013; Kuhlmann et al., 2013; Labudda et al., 2013; Niedtfeld et al., 2013; O'Neill et al., 2013; Rossi et al., 2013). All included studies were well-matched (i.e., no significant differences between patient and control group) for age and gender (see Table 1). Among the included studies, the youngest participant mean age was 16 and the oldest participant mean age was 38, thus restricting our analyses to BPD patients compared to matched controls between the ages of 16 and 38.

3.2 Regional differences in GMV

The results of the ES-SDM meta-analysis of regional GMV of BPD patients compared to healthy controls are presented in Table 2. This meta-analysis demonstrated that individuals with BPD pathology had significantly more GMV than healthy control subjects in a large cluster within the right supplementary motor area (SMA; MNI peak coordinate: $x = 12$, $y = -10$, $z = 66$; $\text{SDM-Z} = 1.017$; 148 voxels). Additionally, BPD patients demonstrated significantly less GMV than controls in a large cluster comprising the right superior and middle temporal gyri (MNI peak coordinate: $x = 56$, $y = -38$, $z = 16$; $\text{SDM-Z} = -1.924$; 212 voxels), a medium-sized cluster comprising the left lingual gyrus (MNI peak coordinate: $x = -16$, $y = -80$, $z = 0$; $\text{SDM-Z} = -2.148$; 107 voxels), and two smaller clusters positioned within the right inferior frontal gyrus pars opercularis (MNI peak coordinate: $x = 52$, $y = 12$, $z = 8$; $\text{SDM-Z} = -1.854$; 15 voxels) and left hippocampus (MNI peak coordinate: $x = -26$, $y = -6$, $z = -22$; $\text{SDM-Z} = -1.785$; 10 voxels). All

these findings were found to be robust as they were significant in at least six of the nine combinations in the jackknife sensitivity analysis.

3.3 Meta-regression analysis: age effects

The results of the ES-SDM meta-regression analysis examining neuroanatomical changes related to age of BPD patients relative to control subjects between the ages of 16 and 38 are presented in Table 3 and illustrated in Figure 2. With increasing mean age, the observed GMV deficit in the left superior parieto-occipital gyri in BPD patients compared to controls disappears (MNI peak coordinate: $x = -24$, $y = -82$, $z = 46$; $\text{SDM-Z} = 3.172$; 162 voxels). Meta-regression additionally showed that initially normal GMV (compared to controls) in the right amygdala in BPD patients decreases with age (MNI peak coordinate: $x = 24$, $y = -2$, $z = -8$; $\text{SDM-Z} = -2.627$; 41 voxels); however, when removing the study by Rossi et al. (2013), this finding was no longer significant.

3.4 Supplemental analyses

Neither percentage of BPD patients currently taking psychotropic medications nor MRI spatial smoothing were significantly associated with regional GMV differences between patients and controls according to meta-regression analyses. Subgroup analysis of MRI field strength showed that studies using 3T scanners were more likely to detect higher GMV in the left insula and right putamen and lower GMV in the left superior and middle parieto-occipital gyri, dorsolateral superior frontal gyrus, and hippocampus than studies using 1.5T and 2T scanners. Additionally, subgroup analyses showed that studies with corrected rather than uncorrected data were more likely to detect higher GMV in the SMA bilaterally. Furthermore, upon repeating the meta-analysis following the removal of a single study measuring gray matter density rather than gray matter volume (Soloff et al., 2008) the main effects of higher right SMA GMV and lower

right superior temporal GMV disappeared, suggesting that the application of a morphometric index detecting volumetric abnormalities at a primarily mesoscopic rather than macroscopic scale may have contributed to these findings (Radua et al., 2014a).

Meta-regression analyses showed that current PTSD was associated with lower GMV in the left hippocampus and higher GMV in the right superior temporal gyrus. Other anxiety disorders were associated with similarly abnormal hippocampal and superior temporal GMV as well as lower and higher GMV in the left dorsolateral superior frontal gyrus and right inferior frontal gyrus pars opercularis, respectively. Substance use disorders were associated with lower GMV in the right superior occipital gyrus, right precuneus, and left inferior orbitofrontal gyrus as well as higher GMV in the right superior temporal gyrus and left amygdala. Depression was associated with lower GMV in the left inferior parietal and middle occipital gyri.

4. Discussion

Although a meta-analysis comparing regional GMV in BPD patients to matched controls has been recently conducted (Schulze et al., 2015), our meta-analysis focused specifically on aging and discussion of meta-regression findings in terms of a neurodevelopmental framework. There are a few methodological differences between our study and that conducted by Schulze et al. (2015) which might have contributed to some differences in findings. First, Schulze et al. included an original statistical parametric map for the study by Niedtfeld and colleagues (2013). Second, results of meta-regression analyses in Schulze et al. were restricted to brain regions showing abnormalities in the group analysis. Third, these meta-regression results were required to be present both in the slope and in one of the extremes of the regressor. Fourth, our meta-analysis included the most liberally-thresholded peak data available from each primary study. Also, a minor difference between our meta-analysis and that conducted by Schulze et al. is that

we included nine rather than ten primary studies: we had to exclude a study in which only ROI data was provided (Völlm et al., 2009) in accordance with our exclusion criteria. However, the data from Völlm et al. (2009) did not appear to influence the results.

4.1 GMV deficits in BPD patients

Like Schulze et al. (2015), we found that BPD patients as a group showed significantly higher GMV in the right SMA and lower GMV in the right inferior frontal gyrus pars opercularis, left hippocampus, and right middle temporal gyri compared to controls. Studies have shown that abnormal right SMA and pars opercularis GMV affect inhibitory control (Hu et al., 2014; Chavan et al., 2015), a neuropsychological domain in which BPD patients frequently exhibit deficit (van Dijk et al., 2014). Low hippocampal GMV has been associated with impaired autobiographical memory function, reactive aggression, and dissociative symptoms and is believed to potentially relate to early life trauma (e.g., childhood abuse) in BPD patients (Zetzsche et al., 2007; Rodrigues et al., 2011). Low right middle temporal GMV has been associated with misinterpretation of social-emotional cues and impaired relational capacity, both of which have been observed in BPD patients (Greimel et al., 2013; Lazarus et al., 2014). In contrast to Schulze et al. (2015), we also found that regional GMV deficit extended to the right superior temporal gyrus. We furthermore found that BPD patients had lower left lingual gyrus GMV than controls. Abnormal left lingual gyrus GMV has been associated with visual attention and memory dysfunction and therefore may contribute to BPD patients' persistent social functioning impairment (Arens et al., 2013; Jung et al., 2014).

4.2 GMV differences associated with age

There are several theories that may account for changes in brain structure over the lifespan in BPD. As conceptualized within the broad biosocial framework of Crowell's model

(Crowell et al., 2009), the combination of our unexpected parieto-occipital and amygdala findings can best be explained by van der Hart's trauma-focused Theory of Structural Dissociation of the Personality as applied to BPD (TSDP; van der Hart et al., 2004). TSDP posits that disrupted early attachment formation with primary caregivers combined with subsequent childhood maltreatment leads the biologically-predisposed temperamentally-sensitive child to suppress negative emotions (e.g., fear, sadness, anger) in favor of only showing positive emotions (e.g., happiness, contentment). This over-awareness of the importance of suppressing negative emotions is an adaptive mechanism most likely employed to win the love and approval from caretakers deemed necessary for survival under conditions of maltreatment (Mosquera et al., 2014). With repeated interpersonal traumas throughout childhood and adolescence, this dissociative defense mechanism becomes automatized, impairing ability to recognize physiological signs of emotional distress (Goodman et al., 2004; van der Hart et al., 2004). This is especially problematic when such individuals experience heightened sensitivity to potentially threatening environmental stimuli along with increased autonomic arousal (Morgan et al., 2006; Barnow et al., 2012). Thus, BPD patients get significantly more activated by environmental stimuli that trigger memories of trauma, since they are unable to recognize the physiological markers of their distress. These tendencies may be related to our finding of delayed GMV development in the left superior parieto-occipital gyri in BPD patients. This interpretation is supported by studies that link low GMV in these regions to prolonged trauma (Tomoda et al., 2009; Qi et al., 2013; Li et al., 2014) and internal state awareness (Wolpert et al., 1998; Nishibayashi et al., 2011). One clinical implication of these findings is the importance of training BPD patients to recognize and self-monitor internal distress cues. Future research might examine

the impact of treatments that include such intervention on changes in parieto-occipital structure and function.

The TSDP model further posits that persistent failure to recognize negative emotions as they occur impairs emotion regulation ability and heightens negative emotionality over time in BPD patients (Troisi et al., 2000; Ford and Courtois, 2014; Mosquera et al., 2014; Sajadi et al., 2015). Our right amygdala finding is likely reflecting this process, as early traumatic stress has been linked to amygdala shrinkage in adulthood possibly due to hypothalamic-pituitary-adrenocortical axis hyper-reactivity (Leichsenring et al., 2011; Pechtel et al., 2014) and low right amygdala GMV has been associated with depression and anxiety (Hayano et al., 2009; van Mierlo et al., 2015). As compared to the left amygdala, the right amygdala typically develops over a longer period of time and therefore may be more sensitive to recurrent trauma during childhood and adolescence (Uematsu et al., 2012). It is important to note that our amygdala finding is not the most robust, as this finding was no longer significant when the study by Rossi and colleagues (2013) was removed from our meta-regression analysis.

4.3 Methodological issues and limitations

There are several limitations to our study that warrant consideration. First, peak-coordinate meta-analyses are based on summarized data rather than raw statistical brain maps. Second, while voxel-based analyses provide excellent control for false positive results, they do not control as thoroughly for false negative results (Radua et al., 2012b). VBM analyses may therefore have insufficient sensitivity to detect between-group differences in small limbic structures (e.g, amygdala, hippocampus) implicated in BPD pathology (Bergouignan et al., 2009). We controlled for this limitation by selecting the most liberally-thresholded coordinate data (uncorrected) whenever available, thus reducing the possibility of missing small limbic

structures. Third, VBM analysis methods have reduced effectiveness at detecting spatially complex and subtle group differences (Davatzikos, 2004); we controlled for this limitation by considering findings and conclusions from primary literature when interpreting our meta-analysis results. Fourth, we were limited by publication bias, as we were unable to include unpublished data in our study. However, the use of voxel-based meta-analysis ameliorates potential bias in favor of specific regions of interest and is likely to provide a more accurate reflection of differences in the brains of BPD patients compared to controls. Fifth, we were limited by the low number of published VBM studies comparing regional GMV of BPD patients versus healthy control subjects.

Finally, the clinically heterogeneous nature of BPD limited specificity of findings. Given that our biosocial conceptualization of BPD has a strong trauma component, the effects of PTSD on neurodevelopment were of particular interest to us. Supplemental meta-regression analysis showed that lower GMV in the left hippocampus was associated with PTSD, consistent with existing literature showing a correlation between chronic stress exposure and small hippocampal volumes (Tottenham and Sheridan, 2009). It is therefore possible that the hippocampal GMV deficit detected in our main effects analysis is primarily attributable to comorbid PTSD rather than BPD. Additionally, in interpreting our parieto-occipital findings, the potentially contributing factor of depression must be considered given the results of our supplemental analyses.

4.4 Conclusion

In sum, the results of this meta-analysis suggest that the neurological underpinnings of BPD are more complex than previously thought. Our detection of abnormal GMV in the SMA and temporal gyri in BPD patients is consistent with previous research, as is our finding of age-related reductions in amygdala GMV. However, according to our results, there appears to be

substantial age-related parieto-occipital GMV abnormalities in BPD patients. These preliminary findings add a new dimension to the biosocial theory of the disorder and highlight the potentially important role that the parietal lobe plays in the neurodevelopment of BPD. Future research should examine brain morphological differences, with special attention to the role of the parietal lobe, in adolescents with BPD and how those differences change as they age.

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Table 1 Characteristics of Studies

Study	Num ber of BPD (fem ale)	Num ber of HC (fem ale)	BPD Age Mean (SD)	HC Age Mean (SD)	Statistics [age]	% patients on psychotro pic medicatio ns ^a	Comorbidit y	MRI Scan ner	Smoot hing	Softw are	Statistica l Threshol d	Covaria tes
Bertsch et al. (2013)	13 (0)	14 (0)	28.9 (10.1)	26.1 (8.3)	$F_{(2,36)} = 0.39, p = .682$ (comparing BPD, HC, and clinical control groups)	8	substance dependence (7) PTSD (1)	1.5T	8mm FWH M	SPM8	$p < 0.005$ (uncorre cted) $k \geq 20$ voxels	none
Brunne r et al. (2010)	20 (20)	20 (20)	16.7 (1.6)	16.8 (1.2)	$F_{(2,57)} = 2.02, p = 0.14$ (comparing BPD, HC, and clinical control groups)	45	mood disorder (9) anxiety disorder (9) substance abuse (9) eating disorder (7) conduct disorder (2)	3T	10mm FWH M	SPM5	$p < 0.05$ (FDR corrected) $k \geq 50$ voxels	none
Kuhlmann et al. (2013)	30 (30)	33 (33)	23.7 (4.6)	24.4 (4.1)	$t_{(61)} = 0.69, p = 0.49$	0	depression (20) PTSD (9) remitted substance abuse (8) anxiety disorder (10) eating disorder (9) adjustment disorder (1) paranoid PD (4) antisocial PD (2) histrionic PD (2) narcissistic PD (2) compulsive PD (2) dependent PD (2) avoidant PD (2)	3T	4mm FWH M	SPM8	$p < 0.05$ (uncorre cted) $k \geq 10$ voxels	total intracra nial head volume

Labudda et al. (2013)	33 (33)	33 (33)	30.51 (11.57)	31.21 (11.03)	$t_{(64)} = 0.25$, $p = 0.80$	48	PTSD (15) major depression (6) panic disorder/agoraphobia (6) bulimia nervosa (5) past substance abuse (3) social phobia (2) OCD (2) GAD (1) specific phobia (1) somatization disorder (1) avoidant PD (6) OCPD (1) dependent PD (1) paranoid PD (1) PD nos (9)	1.5T	12 mm FWHM	SPM5	$p < 0.001$ (uncorrected)	none
Niedtfeild et al. (2013)	60 (60)	60 (60)	29.67 (8.06)	28.5 (7.49)	$t_{(118)} = 0.76$, $p = 0.45$	0	PTSD (21)	3T	10mm FWHM	SPM8	$p < 0.001$ (uncorrected)	age
O'Neill et al. (2013)	20 (20)	21 (21)	32.6 (10.1)	30.1 (8.0)	$t_{(39)} = 0.87$, $p = 0.39$	100	major depression (3)	3T	8mm FWHM	SPM8	$p < 0.001$ (uncorrected) $k \geq 15$ voxels	total brain volume, age
Rossi et al. (2013)	26 (16)	40 (21)	36 (11)	40 (11)	Mann-Whitney U -test value = 1.34, $p = 0.19$	100	depression (5) eating disorder (4) OCD (3) antisocial PD (2) dependent PD (2) alcohol abuse (20) substance abuse (21)	1.5T	8mm FWHM	SPM5	$p < 0.001$ (uncorrected) $k \geq 50$ voxels	education, total intracranial volume, alcohol/substance abuse
Rusch et al. (2003)	20 (20)	21 (21)	29.3 (3.9)	28.4 (6.4)	$t = ns$ (value not reported)	0	dysthymia (15) anxiety (15) PTSD (15)	2T	8mm FWHM	SPM9	$p < 0.001$ (uncorrected) $k \geq 25$ voxels	none

Soloff et al. (2008)	34 (22)	30 (19)	27.5 (8.0)	25.6 (7.7)	$t_{(62)} = 0.95$, $p = 0.35$	0	major depression (7) dysthymia (11) PTSD (2) alcohol use disorder (3) ADHD (1)	1.5T	12mm FWHM	SPM2 prepro cessin g, SPM5 b statisti cal model ing	$p < 0.05$ (FWE corrected)	age, gender
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Note: BPD = borderline personality disorder; HC = healthy controls; SD = standard deviation; PTSD = posttraumatic stress disorder; PD = personality disorder; OCD = obsessive-compulsive disorder; GAD = generalized anxiety disorder; OCPD = obsessive-compulsive personality disorder; ADHD = attention deficit hyperactivity disorder; MRI = magnetic resonance imaging; FWHM = full width at half maximum; SPM = statistical parametric mapping

^areceiving psychotropic medications during and/or one to two weeks prior to MRI scan

Table 2

Results of meta-analysis of VBM studies comparing BPD patients and controls

Anatomical location	MNI peak coordinate <i>x, y, z</i>	Maximum		Cluster		
		SDM-Z value	<i>P</i> value (uncorrected)	Jackknife sensitivity analysis		
				Total cluster size	Breakdown (voxels)	(significant combinations of all 9 combinations)
BPD > HC						
right supplementary motor area, BA 6	12, -10, 66	1.017	0.0014	148	right supplementary motor area, BA 6 (109) left supplementary motor area, BA 6 (13) corpus callosum (7) right supplementary motor area (5) right superior frontal gyrus, dorsolateral, BA 6 (4) left supplementary motor area (3) right cortico-spinal projections (3) left paracentral lobule (2) (undefined) (2)	8 of 9
BPD < HC						
right superior temporal gyrus	56, -38, 16	-1.924	0.0018	212	right superior temporal gyrus, BA 42 (88) right middle temporal gyrus, BA 22 (59) right superior temporal gyrus, BA 22 (36) right middle temporal gyrus, BA 21 (17) right superior temporal gyrus, BA 48 (4) right middle temporal gyrus, BA 42 (4) right arcuate network, posterior segment (2) corpus callosum (1) right superior longitudinal fasciculus III (1)	6 of 9
left inferior network, inferior longitudinal fasciculus (lingual gyrus)	-16, -80, 0	-2.148	0.0005	107	left inferior network, inferior longitudinal fasciculus (97) left lingual gyrus, BA 18 (8) left optic radiations (2)	8 of 9
right inferior frontal gyrus, opercular part, BA 48	52, 12, 8	-1.854	0.0027	15	right inferior frontal gyrus, opercular part, BA 48 (14) right inferior frontal gyrus, opercular part, BA 45 (1)	7 of 9
left hippocampus	-26, -6, -22	-1.785	0.0039	10	left hippocampus, BA 34 (1) left hippocampus (1) left median network, cingulum (1) (undefined) (7)	6 of 9

Note: VBM = voxel-based morphometry; MNI = Montreal Neurological Institute coordinate system; BA = Brodmann area; BPD = borderline personality disorder; HC = healthy controls; SDM = signed differential mapping

Table 3

Age meta-regression slope: regional GMV effect size differences between young BPD patients (i.e. at minimum mean age) *versus* old BPD patients (i.e. at maximum mean age)

	Maximum			Cluster	
Anatomical location	MNI peak coordinate <i>x, y, z</i>	SDM-Z value	<i>P</i> value (uncorrected)	Total cluster size	Breakdown (voxels)
Old > Young					
left superior parietal gyrus	-24, -82, 46	3.172	< 0.0001	162	left superior occipital gyrus, BA 19 (61) left superior parietal gyrus, BA 7 (40) left superior occipital gyrus, BA 7 (19) left middle occipital gyrus, BA 19 (12) left superior parietal gyrus (11) left inferior parietal (excluding supramarginal and angular) gyri (4) left inferior parietal (excluding supramarginal and angular) gyri, BA 7 (3) left superior parietal gyrus, BA 19 (3) left superior occipital gyrus (2) left cuneus cortex, BA 19 (2) left middle occipital gyrus, BA 7 (1) left middle occipital gyrus (1) left inferior parietal (excluding supramarginal and angular) gyri, BA 19 (1) (undefined) (1) (undefined), BA 7 (1)
Old < Young					
right amygdala	24, -2, -8	-2.627	0.0002	41	right amygdala, BA 34 (16) anterior commissure (6) right inferior network, inferior longitudinal fasciculus (6) right striatum (1) (undefined), BA 34 (7) (undefined), BA 48 (5)

Note: GMV = gray matter volume; MNI = Montreal Neurological Institute coordinate system; BA = Brodmann area; BPD = borderline personality disorder; HC = healthy controls; SDM = signed differential mapping

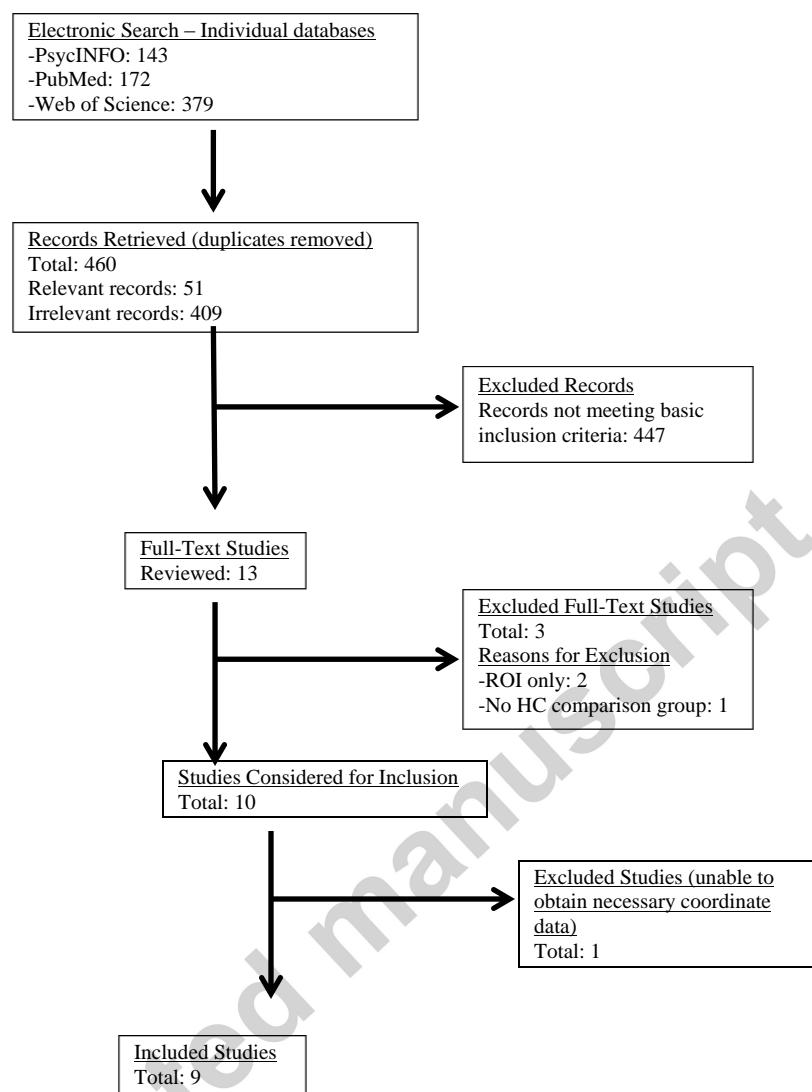


Figure 1. Flowchart of electronic search strategy and inclusion/exclusion of studies

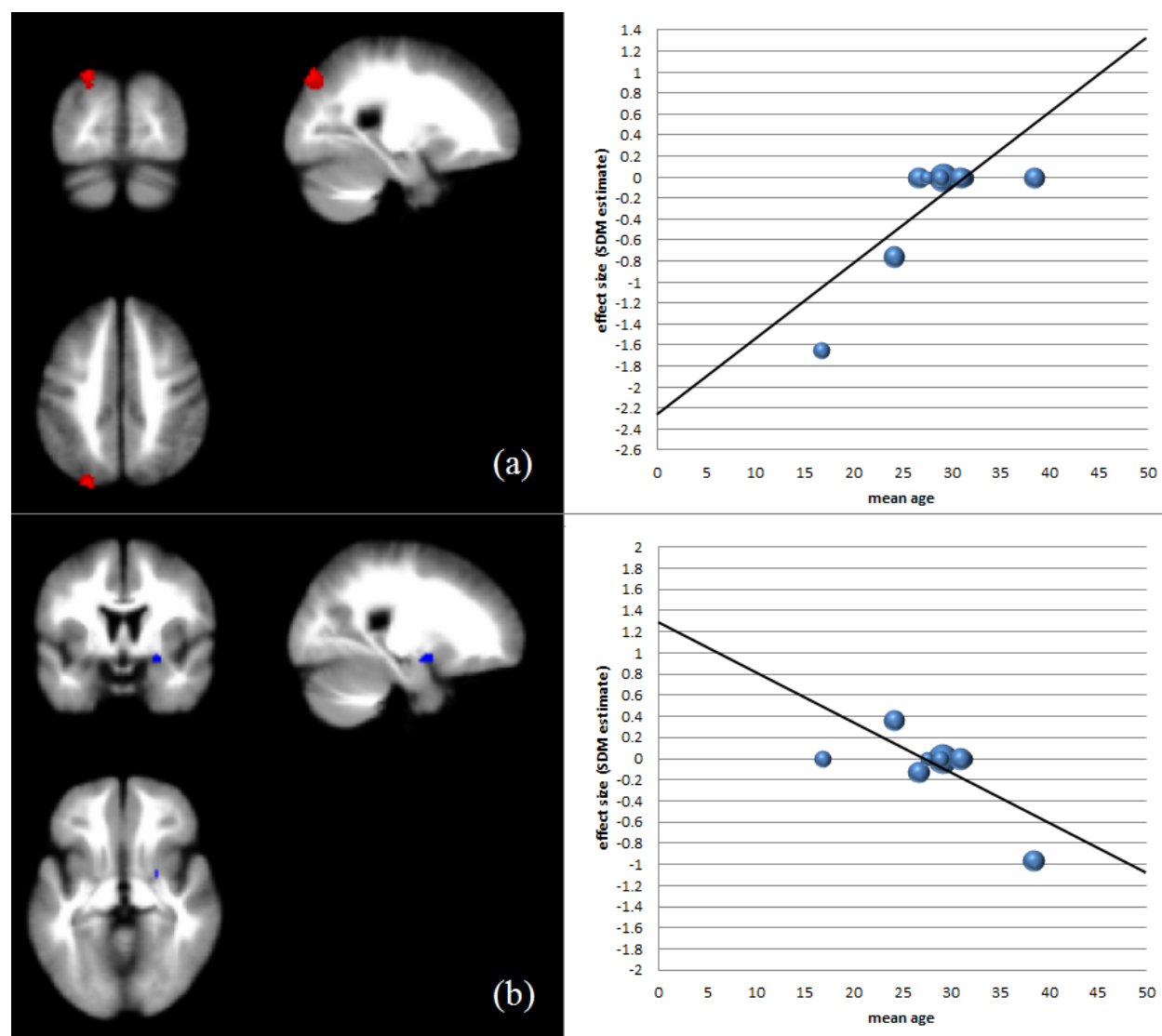


Figure 2. Meta-regression results showing a significant association between increasing mean participant age and (a) increasing GMV in the left superior parieto-occipital gyri (MNI peak coordinate -24, -82, 46) and (b) decreasing GMV in the right amygdala (MNI peak coordinate 24, -2, -8) in BPD patients relative to matched controls. Increasing GMV is indicated in red and decreasing GMV is indicated in blue ($p < 0.0005$, voxels > 20). In the graphs, each study is represented as a dot, with larger dots indicating larger sample sizes. The regression line (meta-regression signed differential mapping slope) is presented as a straight line.

Highlights

- Left superior parieto-occipital volumes increase with age in borderline patients.
- Younger aged borderline patients show significantly lower parieto-occipital volumes.
- Right amygdala volumes decrease with age in borderline patients.
- New dimension added to biosocial theory of borderline personality development.